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AGGLUTINATION IN TYPHUS FEVER*

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The observation has been made by Olitsky[1] that specific agglutinins, precipitins, complement-fixing antibodies, and opsonins for B. typhi-exanthematici (Plotz) are regularly present in the blood of persons convalescent from typhus fever. He reported that "agglutinins (and other antibodies) are usually absent at the height of the disease, but increase in amount at the crisis, until they reach their maximum well along in the apyrexial period."

In the course of further investigations on typhus fever carried on in Volhynia, Russia, during the first 3 months of 1916, at the invitation of the Austro-Hungarian Government, it became necessary to make similar agglutination studies. It has been possible to confirm the observations of Olitsky on much greater material, and to ascertain in more detail the course of the development of antibodies in this disease.

In preparing the tests, the microscopic method was used. The relatively slow growth of the organism and its tendency to clump on standing made the macroscopic method of agglutination impractical. The microscopic tests with this organism, as Olitsky has pointed out, are usually more conservative than the macroscopic.

The technic employed has previously been described. Readings were made after 1 hour, at room temperature, and only a definite agglutination into clumps, with complete cessation of brownian movement, was considered positive. When the clumps were large and there were no free bacteria to be seen between them, the reaction was considered + +. The lowest dilution used was 1 : 50.

Altogether, 271 agglutination tests were made on the serum of 100 persons with typhus fever. In 46 of the patients, from 3 to 8 examinations were made at intervals during the illness and early convalescence.

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These investigations on the typhus fever of Eastern Europe were carried on under the auspices of the American Red Cross by an expedition, consisting of Dr. H. Plotz and the author, which was sent out by the Mount Sinai Hospital. A report of the blood-cultures and a preliminary communication of the studies in prophylactic immunization in Serbia, Bulgaria, and Volhynia, Russia, have already been published (Jour. Am. Med. Assn., 1916, 67, p. 1597; Jour. Infect. Dis., 1917, 20, p. 201).

[1] Jour. Infect. Dis., 1915, 17, p. 20.

The rest were only examined on one or two occasions. Agglutinins were demonstrable in 43 of the 46 cases studied systematically, or in 93%.

Although Olitsky had already reported that agglutinins in dilutions greater than 1:50 are never found in the blood of persons who have not had typhus fever, nor have been exposed to the disease, 28 non-typhus cases were examined as controls for the foregoing observations. They included convalescents from typhoid fever, relapsing fever, acute rheumatic fever, erythema multiforme and variola. All were negative.

No agglutinins were found in the serum of 3 typhus fever patients, examined 4, 5, and 6 times, respectively, during the course of the disease, and early convalescence. A similar failure to develop agglutinins in the blood is occasionally observed after other infectious diseases, such as typhoid. Persons also are encountered who, after repeated inoculations with typhoid, typhus, or cholera vaccines, do not develop agglutinins. Such an experience is not uncommon in animals used for the production of immune serums. Recovery from typhus fever and other infectious diseases is probably due to the consummation of a cellular immunity of the body, and is independent of the development of humoral antibodies. This contention receives still further support from the observation of Denzer and Olitsky,[2] that in contradistinction to man and monkey, the serum of guinea-pigs, after typhus fever, does not contain any agglutinins, precipitins or complement-fixing antibodies, the only immune substances demonstrable being opsonins, and

TABLE 1

RESULTS OF AGGLUTINATION TESTS AT DIFFERENT STAGES OF THE DISEASE

Days of Disease	Number of Examinations	Number Positive	Percentage Positive
1- 4	13	0	0
5- 7	26	8	31
8-11	49	31	63
11-15	49	36	72
Convalescence			
1st week	53	47	88
2nd week	26	25	97
3rd week	20	18	90
After 2 mo.	13	10	77
After 3 mo.	11	6	55
After 10-14 mo.	11	3	27

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[2] Jour. Infect. Dis., 1917, 20, p. 99.

certain specific anaphylactic antibodies demonstrable by the Dale method.

As seen in Table 1, agglutinins are first demonstrable in the blood at about the end of the 1st week of the disease. At this time, agglutinin in more than two-thirds of the cases is still absent. During the 2nd week of the illness over two-thirds of the cases become positive. Agglutination is therefore of some diagnostic value in the latter half of the disease.

The clinical recognition of cases, as a rule, is only difficult at the beginning of the illness. From an epidemiologic standpoint, laboratory aids in diagnosis at this period of the disease are therefore of greater importance. In appreciation of this fact, some of the Austro-Hungarian field laboratories, situated in typhus-infested districts of Volhynia and Russian Poland, are equipped to examine excised specimens of skin, microscopically. But the characteristic changes described by Fraenkel only appear in the skin with the appearance of the rash on about the 5th day of the disease. Such examinations have, therefore, little advantage over the agglutination test.

In the recognition of mild, atypical, and ambulatory cases, agglutination proved to be of greater value. Such cases were frequent in Volhynia, especially among the Russian peasantry, which was undoubtedly often responsible for the spread of disease. The cases found there usually showed a high titer — a point of some importance — and the agglutinins were usually demonstrable in the serum early in the disease, by the 5th or 6th day. *

Olitsky has noted the fact that when a blood culture made during the disease was negative, the serologic examination at that time usually showed a high content of antibodies. In my recent blood-culture studies, I have been able to confirm this. This observation together with the one mentioned would seem to indicate that the early appearance of agglutinins is an evidence of resistance to the disease, and is therefore of prognostic value. Unfortunately, however, the mortality in typhus fever is in part due to complications, chiefly pneumonia, erysipelas, and other infections.

During the early period of convalescence, a great majority of cases showed agglutinins in the blood, the maximum being reached during the 2nd week, when 97% of the examinations were positive. After this, the agglutinins slowly disappeared.

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* In a subsequent paper, the protocols of some of the mild atypical cases will be presented, also those of another group in which agglutinins appeared after exposure to infection, but without the development of any clinical evidences of the disease.

The demonstration of agglutinins in the blood during convalescence, aside from being of value for confirming the diagnosis, was sometimes epidemiologically of considerable importance. By this means we were able to obtain positive evidence of infection in persons suspected of having recently had typhus fever, but who were not seen during the illness. In view of our previous experiences, we were able, therefore, to recognize such recent cases and to recommend isolation until the homes were cleaned up and the lice which they harbored were destroyed.

TABLE 2

RESULTS OF EXAMINATION FOR AGGLUTINATION TITERS ON ONE HUNDRED CASES OF TYPHUS FEVER

Day of Disease	No. of Examinations	Negative	1:50	1:100	1:200	1:400	1:800	Average
1	3	3	0	0	0	0	0	0
2	1	1	0	0	0	0	0	0
3	5	5	0	0	0	0	0	0
4	4	4	0	0	0	0	0	0
5	3	2	1	0	0	0	0	1:17
6	15	9	6	0	0	0	0	1:20
7	8	6	1	0	1	0	0	1:30
8	12	6	6	0	0	0	0	1:25
9	12	4	7	1	0	0	0	1:38
10	12	5	5	1	0	1	0	1:62
11	13	3	7	3	0	0	0	1:54
12	17	4	7	3	3	0	0	1:74
13	9	3	3	0	2	1	0	1:103
14	23	6	6	4	2	5	0	1:135
Convalescence								
Days, 1- 3	31	4	6	4	4	7	1	1:165
Days, 4- 7	22	2	7	3	6	2	2	1:191
Days, 8-14	26	1	8	9	3	2	3	1:199
Days, 15-21	20	2	6	6	3	1	2	1:175
After 2 mo.	13	3	4	3	2	1	0	1:100
After 3 mo.	11	5	2	1	2	1	0	1:91
After 10-14 mo.	11	8	1	1	1	0	0	1:32

The agglutination titers of 271 examinations made on 100 cases of typhus fever have been grouped in Table 2, according to the day of the disease, or period of convalescence on which they were made. The curve (Fig. 1), which has been plotted from the average daily titers in Column 9 of this table, renders a detailed discussion of the results unnecessary. It graphically portrays the average course of the agglutinins in typhus fever.

The agglutination curves of individual cases showed a wide variation from the average. For example, in exceptional cases, a titer of

1 : 50 is found as early as the 5th day of the disease; in others, agglutinins are first demonstrable during the 1st or even 2nd week of convalescence. In the majority of cases, a titer of 1 : 50 appears on about the 10th or 11th day, or about the time when the temperature begins to fall. It then rapidly rises as the temperature approaches normal, the rise usually continuing during the early part of convalescence. The maximum titer (an average of 1 : 200) is reached by the end of the 1st or beginning of the 2nd week of convalescence.

After reaching this height, the titer diminishes slowly, until, in most of the cases, agglutination becomes negative (less than 1 : 50) after 3 or 4 months. However, in 3 cases of the series, the serum still contained agglutinins 12 months after the illness, the titer being 1 : 50, 1 : 100, and 1 : 200, respectively. In the Balkans, Plotz found an agglutination titer of 1 : 200 in a Bulgarian physician who had had typhus fever 2½ years previously.

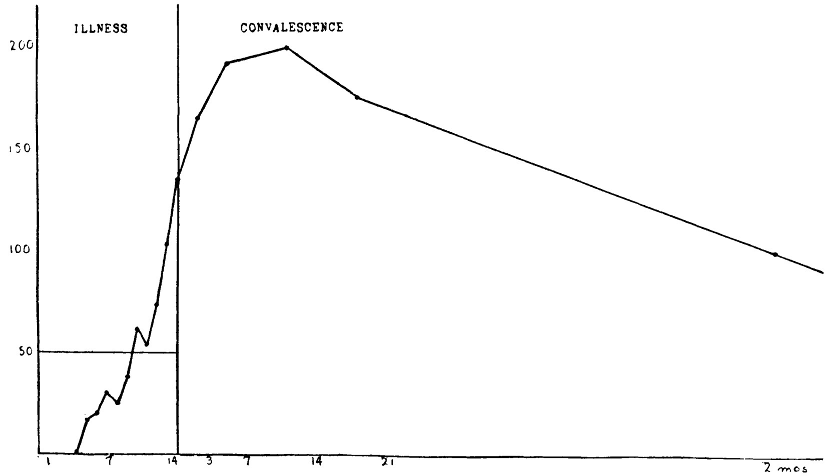

Fig. 1.—Agglutinin Curve in Typhus Fever.

The curve of agglutinins is therefore characteristically an immunity curve. It rises with the recovery and development of immunity, and then persists for a long time, gradually and slowly diminishing. This latter phase is of especial importance in view of recently reported observation of the transitory appearance in the blood during typhus fever of agglutinins for other organisms.

It has been occasionally noted that the Widal reaction may become positive during any febrile disorder in persons who previously had typhoid fever, or who have recently been vaccinated with typhoid bacilli. This seems to be especially common during typhus fever. Many of my patients had a Widal reaction of 1:100-1:200 near the end of the disease, and in all a history of a previous typhoid vaccination, or typhoid fever could be elicited. In one Austrian soldier with typical typhus fever, who had received his last typhoid inoculation 4 weeks previously, the Widal test during the 1st week of the disease was negative. Another test made on the next to the last day of his illness showed an agglutination titer of 1:1600 (macroscopic and microscopic methods). Two weeks after the crisis it had fallen to 1:50, and another examination made just before his discharge from the hospital a week later was negative.

This temporary lighting up of the Widal reaction during typhus fever was commonly observed by the German and Austro-Hungarian army bacteriologists in Russian Poland and Volhynia, for all the troops had received typhoid vaccinations. In 1915, Weil and Felix[3] reported from Volhynia that the serum of persons with typhus fever or recovering therefrom agglutinated a bacillus which they isolated from the urine of 2 patients, and which subsequently proved to be a proteus bacillus. Since then other Austro-Hungarian bacteriologists have confirmed the observation, but have found also that not all proteus-strains are agglutinable by typhus serum, and that occasional strains of the colon bacillus are also agglutinated.

A systematic study with all these organisms including B. typhi-exanthematici has been recently made by Paneth,[4] director of one of the Austrian field laboratories, on about 300 cases of typhus fever. He has found that the agglutinins for the proteus bacillus and the colon bacillus, like those for the typhoid bacillus, are merely transitory. In fact, the curves for the development of agglutinins for these 3 organisms are identical with one another, but are totally different from that for B. typhi-exanthematici. The agglutinins of all 4 organisms usually appear in the blood during the early part of the 2nd week of the disease. The agglutinins for the typhoid bacillus, the colon bacillus, and the proteus bacillus then increase much more rapidly than do those for B. typhi-exanthematici, and reach their maximum at about the time when the temperature of the patient reaches normal. They then diminish rapidly, disappearing from the blood within a few weeks. The agglutination curve for B. typhi-exanthematici, on the other hand, coincided exactly with the one in this paper, the average maximum concentration of agglutinins being reached during the 2nd week of convalescence, the agglutinins then persisting in the blood for many months.

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[3] Wien. klin. Wchnschr., 1916, 29, p. 33.

[4] Verhandl. d. Cong. f. inn. Med., Warsaw, 1916.

The rapid appearance and disappearance of agglutinins for the proteus bacillus, the colon bacillus, and for the typhoid bacillus in persons who have received typhoid vaccine or have had typhoid fever, can only be regarded as a mobilization of preformed antibodies. Their transitory character indicates that after the termination of the typhus fever there is no continued production, as is the case with agglutinins for B. typhi-exanthematici. Their presence in the blood can therefore only be regarded as incidental.

These observations help to explain the fact that specific agglutinins and other antibodies have been found in typhus fever for various aerobic bacteria, previously championed as the causative agents (Müller,[5] Fuerth,[6] Rabinowitsch[7]). They also probably represented mobilization of antibodies performed against any members of the natural flora of the body.

The principle introduced by this observation is of considerable importance. The mere demonstration that in a febrile disease antibodies against a certain bacterium are regularly present in the blood for a brief period does not necessarily imply that that organism is the etiologic agent in the disease. As can be pointed out for many febrile diseases, in which the causative agent is known, it is the continued persistence of humoral antibodies which is usually characteristic and, therefore, of etiologic significance. As Paneth and I have shown for agglutinins, and Olitsky, for agglutinins, precipitins and complement-fixing bodies, the persistence of antibodies for B. typhi-exanthematici in the blood of persons for many months is, therefore, additional evidence that this organism is the causative agent in typhus exanthematicus.

[5] Münch. med. Wchnschr., 1913, 60, p. 1364.

[6] Centralbl. f. Bakteriol., I, O., 1914, 51, p. 79.

[7] Centralbl. f. Bakteriol., I, O., 1909, 52, p. 173. Berl. klin. Wchnschr., 1914, 51, p. 1458.